

The Waning Relationship Between Progression-Free Survival and Overall Survival in Randomized Cancer Therapy Trials

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Abstract

The availability in an increasing percentage of malignancies of a number of active antineoplastic drug strategies has created a situation in which a statistically significant favorable impact of a given anticancer regimen on the time to disease progression in a randomized trial may not be shown to translate into a similar influence on overall survival (OS). This outcome is due to the benefits associated with the uncontrolled, but ethically required, delivery of one or more of these standard-of-care regimens to potentially all trial participants following their removal from the study in question. As a result, it would be highly inappropriate to conclude that a non-statistically significant OS outcome in a randomized trial is evidence for the lack of clinical utility of an investigative approach that has been documented to improve progression-free survival.

Key Words: ovarian cancer, chronic myelogenous leukemia, progression-free survival, second-line treatment of cancer.

The ongoing debate among clinical cancer investigators and other interested parties regarding the most appropriate survival end point in randomized trials (which notably includes intense discussions of the specific requirements for drug regulatory approval) shows no sign of being resolved.¹

The often profound tension accompanying this debate is surely enhanced by the true giant in the room, the growing recognition that unless the entire oncology drug development/payment system paradigm is radically altered, we will as a society simply be unable to afford all antineoplastic therapeutic options that are revealed in evidence-based phase 3 studies to have a positive *P* value for some prospectively defined survival outcome.^{2,3}

In addition, the ongoing and, in fact, accelerating revolution in our understanding of the molecular basis of cancer development, progression, and resistance mandates that the oncology investigative community critically evaluate the existing approaches to drug development and the treatment of individual cancer patients. The days where all patients with advanced/metastatic

breast, lung, or colon cancers were treated with an identical systemic antineoplastic strategy based solely on the anatomic site of origin are long past. Further, the limited size of well-characterized patient populations whose cancers possess well-defined molecular targets makes it increasingly problematic to even consider the conduct of phase 3 randomized trials to define a survival end point—that is, if one would consider it unacceptable for the results of such efforts to be available far more than a decade after study initiation.

It is critically important to add to this discussion the fundamental fact that in many clinical settings, the malignancy can rationally be viewed as a very serious, but more chronic condition, where cure is unfortunately not a realistic expectation of therapy, but where solid evidence demonstrates survival measured in many years, rather than in only a few months. This is objectively a realistic outcome.

Consider, for example, advanced epithelial ovarian cancer. With the exception of several phase 3 randomized trials that demonstrated the favorable impact on survival associated with administering primary (following initial surgical cytoreduction) cisplatin by the intraperitoneal route, compared with the systemic delivery of the agent, the last such frontline study that revealed an improved OS in the malignancy associated with the delivery of a novel agent was the substitution of paclitaxel for cyclophosphamide⁴—and these efforts were conducted almost 20 years ago.

However, it would be profoundly inappropriate to conclude from this factually correct statement that there has been no improvement in ovarian cancer survival over this extended time. In fact, multiple phase 3 trials have revealed “Regimen A” can improve progression-free survival (PFS) compared with “Regimen B,” in a particular setting, but this outcome has not been shown to produce a statistically significant difference in OS between the 2 regimens.

Why not? The answer to this question is clear: There are multiple biologically and clinically active antineoplastic regimens in epithelial ovarian cancer that may be considered for use after progression on a given clinical trial that may favorably impact a patient’s ultimate survival.

With the increasing availability of such active agents/regimens

that may be utilized in this “chronic” condition, it becomes ever more difficult to critically define the unique impact of an individual study regimen on the OS in the malignancy.

Carboplatin/Gemcitabine in Recurrent Ovarian Cancer

The experience with the survival outcomes observed in 2 second-line ovarian cancer carboplatin/gemcitabine chemotherapy trials that were separated in their conduct by approximately 8 years provides a striking example of the influence of subsequent therapies on a patient’s ultimate survival (Table).^{5,6}

While the dangers of cross-trial comparisons are very well-recognized, it should be noted that the 2 studies examined a similar patient population, and there were no obvious differences in the trial design and details. Far more important in assessing the relative comparability of the patient populations entered into the 2 individual studies is the observation that the median PFS results for the 2 studies were essentially identical (Table). However, the OS in the second study was almost twice the duration in the first, suggesting this difference was due to therapies employed after disease progression on the specific carboplatin/gemcitabine trials being evaluated.^{5,6}

In fact, a highly provocative, clinically relevant mathematical model developed by Broglio and Berry⁷ provides strong evidence that the longer the observed post-trial survival, the much larger the study sample size required to demonstrate that a statistically significant improvement in PFS may be translated into a statistically significant improvement in OS. In this analysis, the authors provide an example of a study that required 280 patients to detect a statistically significant 3-month improvement in PFS. Strikingly, if the same relative degree of improvement in OS was desired to be observed, a total sample size of 350 versus 2400 patients would be required if the post-treatment survival was 2 months vs 24 months, respectively. Post-therapy survivals of 24 months (or longer) are now regularly observed following primary treatment of ovarian cancer, and are increasingly common following a variety of second-line therapies.

Imatinib in Chronic Myelogenous Leukemia (CML)

Another highly informative example of an effective post-study treatment impacting OS such that a major impact on PFS fails to be converted to a study-defined improvement in OS is that of the utility of second-line administration of imatinib in CML.⁸ In the landmark study that compared single-agent imatinib with the combination of alpha-interferon plus low-dose cytarabine (the standard of care at the time), a highly statistically significant favorable impact of the novel targeted agent on major cytogenetic response, complete cytogenetic response, and freedom from progression to accelerated-phase or blast-crisis CML was not revealed to result in an improvement in OS in the study population.

Without question, this rather counterintuitive result occurred because of the highly favorable impact associated with second-line imatinib. Therefore, the correct interpretation of the front-line study was not that imatinib failed to improve survival when administered as primary treatment of CML, but rather that both populations of patients (primary or second-line delivery) attained a survival benefit when treated with this important antineoplastic agent.

Recent Innovative Therapeutics in Metastatic Melanoma

An additional poignant example of the impact of subsequent therapies on OS is provided by the recent experience with the delivery of novel therapeutics in metastatic melanoma.⁹ A group of initial trials compared investigative agents with the standard-of-care antineoplastic strategy (single-agent dacarbazine) and revealed a highly statistically significant improvement in PFS that was translated into an improved OS (OS correlation coefficient of 0.96).⁹ In the absence of any even modestly useful second-line treatment, these results were not unanticipated.

However, once crossover to the highly biologically and clinically active new agent was permitted (or one might more appropriately state, ethically mandated)—a strategy that was commonly employed following disease progression on a given trial’s control arm—the relationship between the favorable PFS impact of the study arm and OS was shown to weaken substantially (correlation coefficient 0.55).⁹

TABLE. Survival Following 2 Second-Line Carboplatin/Gemcitabine Chemotherapy Trials in Potentially Platinum-Sensitive Epithelial Ovarian Cancer^{5,6}

		PFS (median)	OS (median)
Carboplatin/gemcitabine	(trial initiated 1999) ⁵	8.6 months	18.0 months
Carboplatin/gemcitabine	(trial initiated 2007) ⁶	8.4 months	35.2 months

OS indicates overall survival; PFS, progression-free survival.

Conclusion

Due to the growing availability of biologically and clinically active antineoplastic agents, it will be increasingly difficult for a specific regimen being examined in a randomized trial to be shown to improve OS, even in the presence of a documented substantial favorable effect on PFS. This outcome results from the delivery of one or more of these alternative strategies following a patient's removal from the study. Further, it would be ethically indefensible to deny a patient known effective treatment solely to obtain trial data regarding OS. It is hoped that this critically relevant issue will be more fully appreciated by the agencies responsible for the regulatory decisions related to antineoplastic drug approval.

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